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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/600,937 | 06/20/2003 | Michael Robin Hale | VPI/98-06DIV | 6239 |

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| EXAMINER | |
|---|---|
| MCKENZIE, THOMAS C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | |

DATE MAILED: 02/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/600,937 | HALE ET AL. | |
| | Examiner | Art Unit | |
| | Thomas McKenzie, Ph.D. | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4,13 and 15-27* is/are pending in the application.

4a) Of the above claim(s) *1,2,4,15,16,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,17 and 19-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. This action is in response to an application filed on 12/21/04. There are seventeen claims pending and eleven under consideration. Claim 13 is a compound claim. Claims 17 and 19 are composition claims. Claims 20-27 are method of using claims. This is the first action on the merits. The application concerns some 1,2-oxazine compounds, compositions, and uses thereof.

### *Election/Restrictions*

2. Applicant's election with traverse of Group III in the reply filed on 12/21/04 is acknowledged. The traversal is on the ground(s) that no search burden is present. Applicants also argue that the compositions could be searched also with the compounds of the elected Group III. This is not found persuasive because according to the MPEP 803 "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant." The Examiner showed that Groups I-VII are in differing classes and Applicants made no showing that the classification analysis was in error. Concerning the argument about compositions, the compounds of the compounds of Group III are included in claim 17, which is a part of the elected Group. If Applicants were urging the

search of the complex compositions of Group VII, then any composition containing a second ingredient, a peptide say, with an earlier US classification would not be searched in a search of the compounds of Group III because that second ingredient would control the classification. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1, 2, 4, 15, 16, and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/21/04.

4. The second compound listed in claim 13 is a 1, 2, 5-oxadiazine not a 1,2-oxazine of the elected invention. 1, 2, 5-oxadiazine are classified in class 544, subclass 66, distinct from the 1,2-oxazine, which are classified in class 544, subclass 63. However, as a courtesy to Applicants, this additional invention was also searched.

5. Objection is made to claims 13, 17, and 19-27 as containing non-elected subject matter. The claims are drawn to multiple inventions for reasons set forth in the above requirement for restriction. The claimed compounds, compositions, and methods that employ them present a variable core. Claim 13 contains compounds drawn to the non-elected inventions.

***Priority***

6. The status of non-provisional parent application should also be included. Since the parent application has become a patent, please update the first line of the specification with the expression "now Patent No. 6,613,743" following the filing date of the parent application.

***Title***

7. After restriction, the title of the invention is no longer descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: replacement deletion of "sulfonamide" by "1,2-Oxazine" since only the first of the six elected compounds is a sulfonamide.

***Abstract***

8. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." The abstract is too short and generic. Examiner suggests claim 13, including the figures, and the utility.

***Claim Rejections - 35 USC § 112***

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13, 17, and 19-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Variable $R^7$ is not defined in claim 13. The definition of variable G in claim 13 is now unnecessary since none of the elected compounds contain this radical.

10. Claims 17 and 19-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 17, 20, 26, and 27 recite the limitation "or a pharmaceutically acceptable derivative" in the last line of each claim. There is no antecedent basis for this limitation in the parent claim 13.

11. Claims 17 and 19-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word derivative is indefinite for we do not know which compounds are contemplated. A derivative is the result of a reaction upon an organic molecule. Since we do not know the reagents or the conditions of these reactions, there is no way of determining the structures of the claimed "derivatives". The phrase "derivative thereof" is, in essence, a product by

process claim. Yet Applicants have not described the intended processes sufficiently that we may understand the structures of the compounds they claim. Webster's New World Dictionary defines derivative as "a substance derived from ... another substance by chemical change", and "substitution of one or more elements or radicals for one or more constituents of the original substance" has occurred. All implying that new chemical bonds have formed. Clearly, some of the "derivatives" obtained from compounds of claim 13, will themselves be covered by those formula. The question is, what compounds falling outside the structural limitations of those formulas are covered under the rubric of "derivatives"?

12. Claims 23 and 24 provide for the use of the compounds of claim 13, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 23 and 24 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153

USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. Applicants are not enabled for the treatment of viruses generally. The search for anti-viral compounds has been slow indeed. The record is filled with new compounds that were highly touted only to show no benefit in human efficacy clinical trials. This reason for this is made clear by the first paragraph in the chapter titled "Antiviral Agents" in "Fields Virology, 3rd Ed." The approaches that have been fruitful take advantage of precisely defined molecular features of the virus and have resulted in effective therapy for herpes and AIDS. As is pointed out in the last paragraph of page 431 of "Fields Virology, 3rd Ed.": "The best

targets for inhibition by antiviral are theoretically molecules serving a function unique to the virus". It is optimistic in the extreme to believe that given the history of anti-viral research that an agent will be effective on such a diverse class of viruses that share physical but not molecular features. The rejected claims call for the treatment of viruses generally. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the treatment of viruses generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17 and 19-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating HIV infections or AIDS with the presently elected compounds. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate

in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The main issues are the lack of any biological testing performed on the presently elected compounds, the nature of the invention, and the unpredictability of enzymatic inhibitory activity.

There is an single *in vitro* assay, drawn to inhibition of the HIV-1 protease enzyme, described in the passage spanning line 11, page 321 to line 2, page 328 with data on the compounds of Formula I. The compounds of formula I are sulfonamides with a mandatory oxygen or nitrogen atom attached to the sulfonamido nitrogen atom. Only the first of Applicants' five elected species is a sulfonamide. Applicants lone sulfonamide compound has a nitrogen atom, not the mandatory heteroatom attached to the sulfonamido nitrogen atom. Thus, the presently claimed species are not structurally related to the compounds of Tables I

and II in the specification, which have demonstrated an ability to inhibit the HIV-1 protease enzyme. The state of the clinical arts in HIV diseases is that inhibitors of this enzyme have shown an ability to treat AIDS and HIV infections.

The nature of the invention requires an understanding of the HIV-1 protease enzyme, the binding activity of small ligands to that receptor, and the ability of those compounds to inhibit HIV-1 protease. In view of the unpredictability of receptor binding activity and claimed divergent compounds with varied polarity, size, and polarisability, the skilled enzymologist would indeed question the inclusion of such diverse compounds, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry. There is no reasonable basis for the assumption that the myriad of compounds embraced the present claim 13 will all share the same biological properties as the compounds of Formula I.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.

Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

15. Claim 23 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for preventing viral infections. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The only established prophylactics are vaccines not the 1,2-oxazine compounds such as present here. In addition, it is presumed that "prophylaxis" of the claimed diseases would require a method of identifying those individuals who will develop the claimed infections before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying

those patients who will acquire the disease before infection occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage in line 29, page 3 states Applicant intend to prevent all viral infections. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical virology and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become infected before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in viral diseases with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of viral diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent viral infections generally. That is, the skill is so low that no compound effective generally against viral disorders has ever been

found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by Claim 13.

The Examiner suggests deletion of the word "prophylaxis".

***Allowable Subject Matter***

16. Claim 13 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action.

***Conclusion***

17. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please

direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

18. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

**Thomas C. McKenzie, Ph.D.**
**Primary Examiner**
**Art Unit 1624**

TCMcK/me